AHRQ Comparative Effectiveness Review Surveillance Program

CER # 23:
Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients with Cystic Fibrosis

Original release date:
October 2010

Surveillance Report 1st Assessment: November, 2011
Surveillance Report 2nd Assessment: August 2012

Key Findings 1st Assessment:

- All conclusions for KQ1-7 are still considered valid
- There are no new significant safety concerns
- Evaluation of the safety and efficacy of recombinant human Insulin-like Growth Factor-I in place of rhGH must await publication of trials.

These findings were unchanged from the 1st assessment

Summary Decision

This CER's priority for updating is **Low** (This is unchanged from the last assessment)

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Effectiveness of Recombinant Human Growth Hormone in the Treatment of Patients with Cystic Fibrosis

1. Introduction

Comparative Effectiveness Review (CER) #23, Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients with Cystic Fibrosis was released in October 2010.[1] It was therefore due for a surveillance assessment in April, 2011. The Surveillance Program commenced in late summer 2010, and the first assessment of CER #23 was submitted in November, 2011. This second assessment was due to start the re-assessment in May, 2012 and was completed in August, 2012.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2010-8/2011 (first assessment) and 8/2011-7/2012 (re-assessment). Initially, this search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and four specialty journals (Journal of Pediatrics, Journal of Cystic Fibrosis, Journal of Clinical Endocrinology, Journal of Clinical Endocrinology and Metabolism, American Journal of Respiratory and Critical Care Medicine, and Pediatric Pulmonology). The specialty journals were those most highly represented among the references for the original report. For Key Questions 1 through 4, 6 and 7, this limited search yielded no relevant titles for the first assessment; therefore, a full Medline search was conducted. Appendix A includes the search methodology for the re-assessment.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER. However, we also accepted for review studies of insulin-like growth factor I for the treatment of cystic fibrosis.

2.3 Expert Opinion

We shared the conclusions of the original report with 11 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; seven subject matter experts responded for the

first assessment. Six of the 7 responded to the reassessment questionnaire. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature searches, the expert assessments, and any reports of the US Food and Drug Administration (FDA), Health Canada, or the United Kingdom's Medicines and Health Care Products Regulatory Agency (MHRA) that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The November 2011 literature search identified 266 titles. After title and abstract review, we further reviewed the full text of 20 journal articles. The remaining 246 titles were rejected because they were editorials, letters, or did not include topics of interest. One additional article was identified while conducting a search to locate one of the original TEP members; this article was too recent to have been included in the results of the search for this report. In addition to the searches, we also reference-mined articles of interest but found no other articles. One further article was reviewed at the suggestion of the experts. Through literature searches, reference mining, and expert recommendations, 22 articles went on to full text review. Of these, six

articles were rejected because they were non-systematic reviews or did not include a comparison of interest. Thus, 16 articles were abstracted into an evidence table (Appendix B).[4-19]

The July 2012 literature search identified 111 articles. After title and abstract review, we further reviewed the full text of five journal articles. The remaining 106 articles were rejected because they were editorials, letters, or did not include topics of interest. One of the 106 had been included in the November 2011 assessment; this article also was suggested by the experts. Of the five articles that went on for full-text review, four were accepted, and one was rejected because it was a systematic review in Portuguese that did not include any studies not already included in the original systematic review we were assessing. Thus, four articles were summarized in the summary table (Table 1) and abstracted into the evidence table (Appendix B).[20-23]

3.2 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signal.

Because meta-analyses were conducted for Key Question 1 in the original CER, and one new study was identified that addressed a number of the outcomes for that question, we also used the Ottawa Method to assess the presence of a signal of the need for an update. A portion of the new findings had already been reported and had been included in meta-analyses conducted for the original report. The findings not included in the original report supported the conclusions of the original report. In addition, the study was not published in a pivotal journal, and the sample size was not larger than that of any studies already included in meta-analyses. Therefore it was concluded that the study did not provide a qualitative signal, and no new meta-analyses were conducted.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
Key Question 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function; growth (height, weight, lean body mass [LBM], protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?					**Previous Assessment**	**Cumulative Assessment**
Pulmonary Function: Absolute FVC: Pooling of 3 RCTs found an improvement with rhGH at 12 months vs. control; 1 single-arm trial found no effect. Percent predicted FVC: Pooling of 5 RCTs found an improvement with rhGH vs. controls. 2 single-arm trials showed mixed results. Absolute FEV1: Pooling of 4 RCTs found an improvement with rhGH vs. control. 1 single arm trial found no effect.	**November 2011** 1 new RCT (open label) showed an increase of 325±319 vs. 178±152 in controls (p=0.032)[24] 1 new RCT showed no change in % predicted FVC and no difference between treated and controls (94 to 95 vs. 102 to 101)[24] 1 new RCT (open label) showed a difference of 115±55 in the adjusted mean increase in FEV_1 from baseline (p=0.041) [24] 1 new RCT showed no change in % predicted FEV_1 and no difference between treated and controls[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** All experts agreed that the conclusions are still valid. Three referred to the Stalvey 2011 study.[24] One expert asked if the search had identified any studies of the use of IGF-1 for CF patients (only 1, a case study, was found). **July 2012** 6 experts responded and agreed the conclusion is still valid	November 2011 Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
Percent predicted FEV1: Pooling of 4 trials found no effect vs. control. 2 single-arm trials found no effect. FEV1 Z-score: 1 RCT showed no effect cf. control.						
Anthropometrics: Height: Pooling of 3 RCTs found an improvement with rhGH vs. control. 1 single arm trial found increase from baseline. Height velocity: Pooling of 3 RCTs found an improvement with rhGH vs. control. 4 single arm trials found an improvement from baseline. Height Z-Score:	**November 2011** No new studies (Stalvey data in original report) **July 2012** No new data **November 2011** 1 new study found a significant difference in height velocity with treatment (2.9 cm [2.0-3.9] or 8.2±2.1 vs. 5.3±1.3) [24] **July 2012** No new data **November 2011** No new evidence **July 2012**	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed the conclusions are still valid; 2 did not respond. **July 2012** 6 experts responded and agreed the conclusions regarding anthropometrics are still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
Pooling of 3 RCTs found an improvement with rhGH vs. control. 3 single arm trials found an improvement from baseline. Height percentile: 1RCT found an improvement with rhGH vs. control. Weight: Pooling of 5 RCTs found an improvement with rhGH vs. control. 1 single arm trial found an improvement from baseline. Weight velocity: Pooling of 2 RCTs found an improvement with rhGH vs. control. 3 single arm trials found no effect. Weight Z-score: Pooling of 4	No new data **November 2011** No new evidence **July 2012** No new data **November 2011** No new evidence **July 2012** No new data **November 2011** No new evidence **July 2012** No new data **November 2011** No new evidence **July 2012** No new data **November 2011** No new evidence					

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
RCTs found no effect with rhGH vs. control. 1 single arm trial found an improvement from baseline. Weight percentile: 1RCT found an improvement with rhGH vs. control. BMI: Pooling of 2 RCTs found an improvement with rhGH vs. control. 1single arm trial found no effect. Percent IBW: Pooling of 2 RCTs found an improvement with rhGH vs. control. LBM: Pooling of 8 RCTs found an improvement with rhGH vs. control.	**July 2012** No new data **November 2011** No new evidence **July 2012** No new data **November 2011** No new evidence **2012** No new data **November 2011** No new evidence **July 2012** No new evidence was identified					

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
Protein Markers: 2 RCTs found mixed results with rhGH vs. control. 1 single arm trial found no effect.	**November 2011** No new evidence **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	November 2011 2 experts stated that they did not know if the conclusion is still valid. One stated that it is still valid. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Exercise Tolerance: 3 RCTs found no effect with rhGH vs. control. 1single arm trial found no effect.	**November 2011** 1 new study using a 6-minute walk found a slight increase in the distance walked from baseline to 12 months (p=0.0437) but not for controls, and no significant difference between treated and controls in the increase from baseline.[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Bone mineralization: Bone age: 2	**November 2011** No new evidence **July 2012**	**November 2011** No new data **July 2012**	**November 2011** 5 experts agreed that the conclusion is still valid. 2	**November 2011** Conclusion is still valid and this portion of the	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
RCTs found no effect with rhGH vs. control. 3 single arm trials found an improvement from baseline. BMC: Pooling of 4 RCTs found an improvement with rhGH vs. control. BMC Z-score: 1RCT found an improvement with rhGH vs. control.	No new evidence was identified November 2011 No new evidence **July 2012** No new evidence was identified **November 2011** No new evidence **July 2012** No new evidence was identified	No new data	did not respond. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know	CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.		
Sexual Maturation: 1RCT found an improvement with rhGH vs. control.	**November 2011** No new evidence **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Key Question 2. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including frequency of required intravenous antibiotic treatments, frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia, or mortality, compared with usual care alone?						
Antibiotic Use: 3 RCTs found an improvement with rhGH vs.	**November 2011** 1 new study found no difference in IV antibiotic use with	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 1 said s/he did not know.	**November 2011** Conclusion is still valid and this portion of the CER does not need	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
control but evidence was considered insufficient.	rhGH vs. controls (2 vs. 1) [24] **July 2012** No new evidence was identified		**July 2012** 6 experts responded and agreed the conclusion is still valid	updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.		
Pulmonary exacerbations: 1 RCT found no effect with rhGH vs. control but evidence was considered insufficient.	**November 2011** 1 new study reported hospitalization for pulmonary exacerbations among 10 rhGH and 9 control participants over 12 months (i.e., no difference).[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 1 said s/he did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Hospitalization rate: Pooling of 4 RCTs found an improvement with rhGH vs. control.	**November 2011** See above. **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 1 said s/he did not know. 1 did not respond. Of those who said the conclusion is still valid, 1 said that the lack of difference Stalvey[24] saw in hospitalization rates could be attributable in the different criteria for hospitalization across study sites and the fact that the study was not powered to detect differences in this	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
			outcome. **July 2012** 6 experts responded and agreed the conclusion is still valid			
HRQoL: 2 RCTs found an improvement with rhGH vs. controls but evidence was considered insufficient	**November 2011** No new studies found **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** n/a **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Bone consequences: no data	**November 2011** No new studies found **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** n/a **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Mortality: no data	**November 2011** No new studies found **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** n/a **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
				updating.		
Key Question 3: In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?						
Mortality: Pulmonary function: 28 observational studies showed mixed results regarding whether improvements in pulmonary function were associated with effects on mortality. Anthropometrics: 26 observational studies showed mixed results regarding whether improvements in	**November 2011** 5 observational studies found that various indices of lung function were associated with a higher risk of mortality.[5, 7, 11-13] One observational study found that pulmonary arterial pressure but not FEV1 was associated with increased mortality.[9] Another study found that 5-year mortality was similar in patients with and without pulmonary HTN however, mortality was higher in patients with left ventricular ejection fraction <55%[11] **July 2012** No new evidence was identified **November 2011** 3 observational studies showed mixed results regarding the	**November 2011** No new data **July 2012** No new data	**November 2011**5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts agreed the conclusion is still valid. **November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
anthropometric measures were associated with effects on mortality. Protein turnover: No studies assessed the association between changes in protein turnover and changes in mortality. Exercise tolerance: 10 observational studies assessed the association between exercise tolerance and changes in mortality, with mixed results. Bone mineralization: No studies assessed this association.	association between BMI and mortality.[9, 12, 13] **July 2012** No new evidence was identified **November 2011** No new studies assessed the association between protein turnover and mortality. **July 2012** No new evidence was identified **November 2011** No new studies assessed the association between exercise tolerance and mortality. **July 2012** No new evidence was identified **November 2011** No studies assessed this association.		**November 2011** 4 experts agreed that the conclusion is still valid. 2 did not respond. 1 said s/he did not know. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know **November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** No new evidence was identified **November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know			

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
	July 2012 No new evidence was identified **November 2011** Other: 2 observational studies identified an association between hyperglycemia or elevated HBa1c and increased risk for death.[6, 13]					
HRQoL Pulmonary function: 14 observational studies showed improvements in pulmonary function were associated with improved HRQoL. Anthropometrics: 10 observational studies showed mixed results regarding	**November 2011** 2 observational studies assessed association of worsening pulmonary function with QoL: in one, in youth under 14, worsening pulmonary function was associated with decreased QoL scores[10]; in youth ≥14 and in the other study, changes in lung function were not associated with changing QoL scores.[8, 10] **July 2012** No new evidence was identified **November 2011** No new studies assessed other	**November 2011** No new data **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. 1 said s/he did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid **November 2011** 4 experts agreed that the conclusion is still valid. 1 said s/he did not know. **July 2012** 6 experts responded and	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating. **November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012**	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
whether improvements in anthropometric measures were associated with effects on HRQoL. Protein turnover: No studies assessed this association Exercise tolerance: 2 observational studies showed improvements in exercise tolerance were associated with improved HRQoL.	associations **July 2012** No new evidence was identified		agreed the conclusion is still valid **November 2011** 4 experts agreed that the conclusion is still valid. 1 said s/he did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid **November 2011** 3 experts agreed that the conclusion is still valid. 1 said s/he did not know. 1 cited a newer study showing decreased QoL with an exercise program that increased exercise tolerance (but the study did not meet inclusion criteria, as it implemented an intervention) **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know	Conclusion is still valid and this portion of the CER does not need updating. **November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating. **November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.		

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
Bone mineralization: No studies assessed this association.						
Bone Consequences Pulmonary function: 1 observational study showed no association between improvements in pulmonary function and improved bone consequences. Anthropometrics: 1 observational study showed no association between improvements in anthropometrics and improved bone consequences. Protein turnover: No studies assessed this	**November 2011** No new studies assessed these associations **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. 2 said they did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid **November 2011** 3 experts agreed that the conclusion is still valid. 2 said they did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid **November 2011**	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating. **November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
association. Exercise tolerance: No studies assessed this association. Bone mineralization: No studies assessed this association.			3 experts agreed that the conclusion is still valid. 2 said they did not know. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know **November 2011** 3 experts agreed that the conclusion is still valid. 2 said they did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid **November 2011** 3 experts agreed that the conclusion is still valid. 2 said they did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating. **November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating. **November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid		

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
				and this portion of the CER does not need updating.		
Key Question 4. In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH? Adverse effects of interest include, but are not limited to, glucose intolerance, diabetes, and hypoglycemia.						
Glucose Parameters: A1c: 2 pooled RCTs found no effects with rhGH vs. control. 2 single arm trials found no effect. Random BG: 3 RCTs found no effects with rhGH vs. control. Fasting BG: 2 pooled RCTs found increased fasting BG with rhGH vs. controls. 1 single-arm trial found no effect. Stimulated BG: 1 RCT found no effect of rhGH. Postprandial BG: 1 RCT found no	**November 2011** In 1 new RCT, 100% of tx and 97% of controls reported at least one adverse event (AE). 12 participants in each group experienced a serious AE, mostly pulmonary exacerbations. 10 tx participants reported a study drug-related AE.[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. 1 said s/he did not know. 1 mentioned that the significance of elevated fasting blood glucose levels is unclear and may not be clinically significant. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
increased risk with rhGH.						
Glucose Intolerance: 7 RCTs found no increased risk with rhGH.	**November 2011** In 1 new RCT, 5 rhGH recipients reported hyperglycemia (of whom 1 dropped out)[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. 2 said they did not know. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Diabetes: 7 RCTs found no increased risk with rhGH.	**November 2011** No new evidence **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Injection Site Reactions: 2 single-arm trials found minor discomfort and bruising with rhGH	**November 2011** In 1 new RCT, 7 rhGH recipients reported injection site reactions.[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Liver Transaminases: 2 single-arm trials found	**November 2011** No new evidence **July 2012** No new evidence was	**November 2011** No new data **July 2012** No new data	**November 2011** n/a **July 2012** 6 experts responded and	**November 2011** Conclusion is still valid and this portion of the CER does not need	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
limited reporting of liver transaminase elevations.	identified		agreed the conclusion is still valid	updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.		
Study Withdrawals: Of 10 RCTs, most reported no withdrawals	**November 2011** In 1 new RCT, at least 2 study withdrawals were attributed to drug-related AEs.[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** n/a **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
	November 2011 Other: In one new RCT, 1 case of papilledema and headache was reported (resulting in dropping out, most likely benign IH). 1 participant died of respiratory failure at 15 months, reported as unrelated to study drug.[24] **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 1 expert mentioned the report of papilledema and headache in Stalvey 2011[24] **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Key Question 5. What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (insulin-like growth factor-I [IGF-I] increases over 100 ng/ml or insulin –like growth factor binding protein-3 [(IGFBP-3] decreases over 1,000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2 mg/kg/week to 0.6						

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
mg/kg/week) for disorders such as growth hormone deficiency (GHD) and idiopathic short stature (ISS)?						
Biomarkers: IGF-1: 4RCTs found higher IGF-1 in the rhGH group than among controls. IGFBP-3: 1RCT found higher levels with rhGH treatment.	**November 2011** IGF-1: 1 new RCT reported increases in IGF-1 in treated CF patients vs. baseline and vs. the increase in controls at 6- and 12-months of treatment but these increases did not persist at 18 months.[24] 1 new retrospective case control study of patients with and without malignancies in the KIMS database showed increased IGF-1 Z-score levels associated with neoplasms only in those under 40 years of age (n=10). However, with multivariate analysis, IGF-1 levels were not elevated.[17] Same study (subsequent publication) showed that IGFBP-2 and 3 Z-scores were higher in the malignancy group also and remained	**November 2011** On 8/17/11, the FDA updated a Drug Safety Communication of 12/2010 to issue the results of its review of a study conducted in France that suggested an increased risk of death associated with the use of rhGH. Along with other sources, the new study did not provide evidence suggestive of a link between rhGH and increased risk for death (http://www.fda.gov/Drugs/DrugSafety/ucm265865.htm) **July 2012** No new data	**November 2011** 3 experts agreed that the conclusion is still valid. 1 said s/he did not know. 1 also cited the new Stalvey study,[24] which corroborates earlier findings. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
	high with multivariate analysis.[14] **July 2012** No new evidence was identified					
Cancer Incidence in CF Patients: No RCTs were identified. 1 case report identified a probable relationship between rhGH and cancer.	**November 2011** No new RCTs were identified. **July 2012** No new evidence was identified	**November 2011** No new data **July 2012** No new data	**November 2011** 4 experts agreed that the conclusion is still valid. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Cancer Incidence in Non-CF Patients: No RCTs were identified. 3 single-arm studies provided insufficient data to draw any conclusions.	**November 2011** 4 cohort studies examined rates of malignancy among non-CF patients under GH treatment.1) A study of KIMS (adult) patients found recurrence of pituitary or CNS tumors in 6 (1.4%) patients; recurrence of other neoplasias: 11 (2.5%) patients.[14] 2) Among 55,000 children followed in the National Cooperative Growth Study, the most common cause of	**November 2011** No new data **July 2012** No new data	**November 2011** 4 experts agreed that the conclusion is still valid. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
	death was CNS tumor (recurrence or new onset). 11% of deaths were judged to be related to rhGH by investigator (4 were not assessable and no causality was provided for 21: 19 of the 21 were due to neoplasms [1 osteosarcoma recurrence, the rest were CNS-related]). A total of 243 intracranial malignancies of non-pituitary origin, 199 recurring and 44 new onset, were reported. 87 extracranial malignancies (including leukemia), 24 recurring and 63 new onset (42 of which were associated with previously defined risk factors) were also reported. Leukemia: 27 cases reported (9 recurrent,15 new, and 3 that developed after rhGH discontinuation; SIR for new-onset leukemia without prior risk factors=0.54					

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
	(0.11, 1.58) Second neoplasms: 49/2500 patients with a history of malignancy (most commonly leukemia) developed a second tumor (most commonly glioblastoma/glioma, osteogenic sarcoma, astrocytoma, leukemia, meningioma, mucoepidermoid carcinoma; calculated rhGH exposure time was 4.3 yr.[15] 3) A prospective study that followed over 50,000 children treated with rhGH for growth deficiency (in the KIGS database) who had no risk factors for cancer development found no significant difference in the rate of tumor development from that of the general population.[18] 4) A study of 110 adult patients who underwent rhGH therapy after radiation					

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
	for intracranial tumors found no difference in the rate of recurrence or new tumor development compared with untreated age-matched controls.[16] **July 2012** 4 reports of 3 new observational studies assessed the association between hGH treatment and cancer. One case study reported an incidence of intracranial endodermal sinus tumor in a 15-year old girl who underwent GH replacement therapy for 17 months.[23] The EU SAGhe Study reported no cancer deaths among persons treated with rhGH as children in the Netherlands, Belgium, or Sweden[22] but an increase in deaths due to osteosarcoma in France[20]. A short follow-up study of hypopituitary adults treated with hGH					

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
	found no increased risk of cancer.[21]					
Key Question 6: In patients with CF, how are efficacy, effectiveness, safety, or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?						
Dose: 1 RCT found no differences between dose groups in endpoints	**November 2011** No new studies were identified. **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded; 5 agreed the conclusion is still valid, 1 said he did not know	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Duration: 9 pooled RCTs identified a trend toward increased efficacy for 1-year therapy vs. 6-month therapy	**November 2011** No new studies were identified. **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts agreed the conclusion is still valid, but one noted that in the original report, the conclusion should have been that 6 months of treatment did result in a significant increase in height	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Baseline Nutrition Status: 1 RCT provided limited evidence regarding efficacy in patients with	**November 2011** No new studies were identified. **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded and agreed the conclusion is	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
variable nutrition status; rhGH is efficacious in patients receiving enteral therapy.			still valid	and this portion of the CER does not need updating.		
Concurrent Medical Therapies: No studies were identified.	**November 2011** No new studies were identified. **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 2 did not respond. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Key Question 7: In patients with CF, how do the efficacy, effectiveness, safety, or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to, age (prepubertal, pubertal, postpubertal), gender, baseline clinical status (height, weight, LBM, pulmonary function, exercise tolerance, nutritional status), and/or the nature, extent, and effectiveness of prior treatment.						
Age: 6 pooled RCTs found that adolescents (postpuberty) may derive greater benefit from rhGH with respect to pulmonary function, weight, and bone mineral content than prepubertal patients; however, prepubertal	**November 2011** One new RCT that enrolled only children<14 years of age reported an increase in FVC and a trend toward increased FEV1.[24] **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 5 experts agreed that the conclusion is still valid. 1 said s/he did not know. 1 cited the Stalvey 2011 finding of increased pulmonary function in children under 14 who were treated with rhGH. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
patients may derive greater benefit in height vs. adolescent patients.						
Sex: 3 pooled RCTs found that females (both pre- and postpubertal) may derive greater benefit in height and weight than males	**November 2011** No new studies were identified **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 4 experts agreed that the conclusion is still valid. 3 did not respond. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Baseline Clinical Status: 2 RCTs found that patients with lower baseline height Z-scores experienced greater height improvement than those with higher height Z-scores; higher baseline weight was correlated with greater improvement in pulmonary function.	**November 2011** No new studies were identified **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	**November 2011** 4 experts agreed that the conclusion is still valid. 3 did not respond. **July 2012** 6 experts responded and agreed the conclusion is still valid	**November 2011** Conclusion is still valid and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.	Up-to-date	Up-to-date
Prior Treatment: No studies were	**November 2011** No new studies were	**November 2011** No new data	**November 2011** 4 experts agreed that the	**November 2011** Conclusion is still valid	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
identified.	identified **July 2012** No new studies were identified	**July 2012** No new data	conclusion is still valid. 3 did not respond. **July 2012** 6 experts responded and agreed the conclusion is still valid	and this portion of the CER does not need updating. **July 2012** Conclusion is still valid and this portion of the CER does not need updating.		
Studies of relevance that did not directly respond to a key question						
	November 2011 A new case study found that treatment of a boy with CF with IGF-1 resulted in improved growth velocity after concurrent GC therapy was terminated. Body weight increased about 10kg, marked improvement in FEV1; decrease in HbA1c. In addition, he was able to d/c insulin, GC, and antibiotics.[4] **July 2012** No new studies were identified	**November 2011** No new data **July 2012** No new data	n/a	n/a	Up-to-date	Up-to-date

Legend: BMI Body mass index; CF cystic fibrosis; d/c discontinue; FEV1 forced expiratory volume in 1 second; FVC forced vital capacity; GC glucocorticoid; HBA1c hemoglobin A1c; HRQoL health-related quality of life; IH intracranial hypertension; IGF-I insulin-like growth factor I; IGFBP insulin-like growth factor binding protein; LBM lean body mass; MHRA Medicines and Healthcare products Regulatory Agency; RCT randomized controlled trial; rhGH recombinant human growth hormone

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed (7/1/2011-6/22/2012)

LANGUAGE:
English

SEARCH STRATEGY #1 (KQ1 - HUMAN GROWTH HORMONE):
cystic fibrosis[mh] OR cystic fibrosis[tiab]
AND
human growth hormone[mh] OR human growth hormone[tiab] OR recombinant human growth hormone OR rhgh OR hgh OR somatropin OR genotropin OR humatrope OR hypertropin OR jintropin OR nordotropin OR nutropin OR omnitrope OR saizen OR serostim OR zomacton OR zorbtive OR crytropin

NUMBER OF RESULTS: 8

SEARCH STRATEGY #2 (KQ3 – INTERMEDIATE OUTCOMES):
cystic fibrosis[mh] OR cystic fibrosis[tiab]
AND
epidemiologic studies[mh] OR case control studies[mh] OR cohort studies[mh] OR "case control"[tiab] OR "cohort study"[tiab] OR "cohort studies"[tiab] OR cohort* OR "follow up" OR "follow-up" OR observational OR longitudinal OR retrospective OR cross sectional OR cross-sectional OR cross-sectional studies[mh] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy OR randomly[tiab] OR trial[tiab] OR groups[tiab]
AND
mortality[mh] OR death OR quality of life[mh] OR "quality of life" OR qol OR fractures, bone[mh] OR "bone fracture*" OR "broken bone*" OR neoplasms[mh] OR neoplas* OR malignan* OR cancer OR cancers OR cancerous OR tumor OR tumors OR tumour OR tumours

NUMBER OF RESULTS: 108

SEARCH STRATEGY #3 (KQ5 – RISK OF MALIGNANCY):
human growth hormone[mh] OR human growth hormone[tiab] OR recombinant human growth hormone OR rhgh OR hgh OR somatropin OR genotropin OR humatrope OR hypertropin OR jintropin OR nordotropin OR nutropin OR omnitrope OR saizen OR serostim OR zomacton OR zorbtive OR crytropin
AND
epidemiologic studies[mh] OR case control studies[mh] OR cohort studies[mh] OR "case control"[tiab] OR "cohort study"[tiab] OR "cohort studies"[tiab] OR cohort* OR "follow up" OR "follow-up" OR observational OR longitudinal OR retrospective OR cross sectional OR cross-sectional OR cross-sectional studies[mh] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy OR randomly[tiab] OR trial[tiab] OR groups[tiab]
AND
mortality[mh] OR death OR quality of life[mh] OR "quality of life" OR qol OR fractures, bone[mh] OR "bone fracture*" OR "broken bone*" OR neoplasms[mh] OR neoplas* OR malignan* OR cancer OR cancers OR cancerous OR tumor OR tumors OR tumour OR tumours
AND
"idiopathic short stature" OR iss[tiab] OR "growth hormone deficiency" OR ghd OR "gh deficiency"

AND
neoplasms[mh] OR neoplas* OR malignan* OR cancer OR cancers OR cancerous OR tumor OR tumors OR tumour OR tumours

NUMBER OF RESULTS: 20

Appendix B. Evidence Table

Article ID / Cohort/First Author/Year	Participants (age, sex, condition)/ Sample size	Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Primary Outcome/ Method of Ascertainment	Study Quality/Applicability	Findings
Key Question 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function; growth (height, weight, lean body mass [LBM], protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?						
Stalvey, 2011[24]	68 children<14 yoa with CF	Inclusion criteria: • Hx of CF, • ages 5-12 (girls) and 5-13 (boys), • height≤10th percentile for age and sex; • bone age≤10 yrs for girls and 11 years for boys • prepubertal status (Tanner stage 1) • ability to reproducibly perform pulmonary fn tests • normal thyroid fn; • adequate caloric intake Post-hoc analysis adjusted for baseline	Multi-center, open-label, controlled clinical trial randomized 68 participants to receive rhGH 12 months, followed by 6 months followup	Primary: ΔLBM, Height Std. Deviation Score (SDS) Secondary: Height weight, FvC, FEV_1, exercise tolerance, glucose tolerance, IGF-1, preplanned list of AEs Ascertainment: Dx by sweat test (chloride>60mmol/L) or genetic testing,	Jadad 3 Applicability 4 of 7	Growth (annualized height velocity at month 12) 8.2±2.1 cm/yr for rhGH group and 5.3±1.3cm/yr for controls (p<0.0001) Mean change from baseline in SDS was significantly greater for treated than controls and greater for treated at month 12 than at baseline (p<0.0001). IGF-1: treated> controls at months 6 and 12 but not at month 18 (after 6 months off treatment) Δ Body weight: at month 12, mean delta body weight treated was greater than baseline and

Article ID / Cohort/First Author/Year	Participants (age, sex, condition)/ Sample size	Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Primary Outcome/ Method of Ascertainment	Study Quality/Applicability	Findings
		differences between treated and control group (FEV1, FVC, and distance walked in 6 minutes were all lower in the rhGH group@ baseline) Exclusion: impaired glucose tolerance				greater than control (3.8±1.8 vs. 2.8±1.5,p=0.0356) Δ Lean body mass: Tx > controls (1.8kg, 95% CI: 0.9, 2.7, p<0.0002), although both groups had significant increases from baseline to 12 months ΔLBM as % total body composition was not significant. Adjusted FVC mean change from baseline tx> controls (P=0.0318) Adjusted FEV_1 improvement from baseline in tx> controls(p-0.04) Pulmonary Exacerbations: No significant differences between treatment groups 99 controls and 10 tx required hospitalization) Six-minute walk:

Article ID / Cohort/First Author/Year	Participants (age, sex, condition)/ Sample size	Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Primary Outcome/ Method of Ascertainment	Study Quality/Applicability	Findings
						Tx group increased by 10% (p=0.0437); no significant increase in control group; no significant difference in change from baseline to 12 months between groups. Glucose Tolerance: Fasting glucose increased in the tx group (p<0.05) by month 12 but not in the control group. Fasting insulin rose in both groups.

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Haupt, 2011[4]	1 male youth, age 16 years on insulin, antibiotics, and glucocorticoid therapy following liver transplant	CF diagnosed at birth by sweat test and genetic testing	Case study of rhIGF-1 administration	Height velocity, change in body weight, FEV1, HbA1c	N/A	Growth velocity improved after GC therapy was terminated. Body weight increased about 10kg, marked improvement in FEV1; decrease in HbA1c. In addition, he was able to d/c insulin, GC, and antibiotics
Key Question 2: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including frequency of required intravenous antibiotic treatments, frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia, or mortality, compared with usual care alone?						
Stalvey, 2012[24]	See KQ1	See KQ1	See KQ1	See KQ1	See KQ1	9 control participants and 10 rhGH participants required hospitalization for pulmonary exacerbations; an additional control participant and 2 rhGH participants required IV antibiotics

Article ID / Cohort/First Author/Year	Participants (age, sex, condition)/ Sample size	Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Primary Outcome/ Method of Ascertainment	Study Quality/Applicability	Findings
Key Question 3: In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?						
Mortality/ Survival						
De Boer, 2011[5]	446 adults (255 males) w/CF 140 had less than 1 pulmonary exacerbation/yr 160 had 1-2 exacerbations/yr 146 had more than 2 exacerbations/yr	CF diagnosed via genetic testing or sweat test	Prospective cohort study to determine whether more frequent pulmonary function exacerbations (or any other factors) are associated with accelerated functional decline or progression to lung transplant or death	FEV1, lung transplant, mortality over 3 years	n/a	Female sex, diabetes, and poorer baseline lung function were associated with increased risk for exacerbations. Patients with >2 exacerbations were more likely to experience a 5% decline from baseline in FEV_1 (adjusted HR 1.55 (95% CI1.10, 2.18, p=0.01) and an increased risk of lung transplant or death (adjusted HR 4.05, 1.15, 14.28, p=0.03) or 3-year risk of death (unadj. HR 7.86, 1.81, 34.2, p=0.006) over the 3 years of the study
George, 2011[7]	276 patients (147 male; mean age 25.9)	FEV1 less than 30% of the predicted value for	Observational (prospective cohort study)	Survival rates from 1990 to 2007 and association with		Overall, survival improved from 1994 to 1997 but

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	seen between 1990 and 2003, from among all CF patients referred to CF unit at a British hospital during that time	their height, sex, and age CF diagnosed clinically or via genetic testing or sweat test		particular risk factors		not thereafter. Death was associated with body mass index <19 (adjusted HR1.52, 95% CI 1.10, 2.10, p=0.011); use of nebulized antibiotics (HR 1.84, 95% CI 1.05, 3.22, p=0.033); and use of long term oxygen therapy HR 3.52 (95% CI 2.49, 4.99, p<0.001)
Chamnan, 2010[13]	8,029 patients in UK Cystic Fibrosis Registry (1996-2005), of whom 5,892 patients were included in analysis.	Participation in registry	Retrospective cohort study	Risk factors associated with death in CF patients, including age, sex, ethnicity, BMI, pulmonary function, **diabetes**, respiratory infection, class of CF transmembrane conductance regulator alleles, dx of CF by neonatal screening, prior organ transplantation,		For 17,672 person-years of follow-up, 393 subjects died. Age-adjusted mortality rates were 4.2 (3.4-5.1) in individuals with diabetes, and 1.5 (1.3-1.7) in those without diabetes. Independent risk factors for death included diabetes, female sex, poorer pulmonary function, lower BMI, B. cepacia infection, absence

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						of S. aureus infection, allergic bronchopulmonary aspergillosis, liver disease, prior organ transplantation, and corticosteroid use. Better or less delayed tx for diabetes might extend survival.
Adler, 2011[6]	5,810 patients in UK Cystic Fibrosis Registry (2006-2009), of whom 912 had diabetes and full clinical data were available for 520. Median age 25.0 (range 0.4-67.8)	Participation in registry	Retrospective survival analysis study/hyperglycemia, defined as HbA1c≥6.5 (vs. <6.5)	Mortality		84% of patients were receiving medication to control blood glucose. Hyperglycemic patients did not differ with respect to age, sex, BMI, pulmonary fn, or use of corticosteroids. During a median follow-up of 2.01 years (0.02-3.53), 36 patients died. Their median HbA1c was higher than in survivors (7.3% vs. 6.7%) (HR 3.2, 95% CI 1.4, 7.3, p=0.005) Controlling for risk

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						factors for death conceivably related to hyperglycemia (age, sex, BMI z score, FEV1, use of corticosteroids) did not change the association (HR for multivariate analysis 3.3, 1.4-7.5; p=0.005).
Baghaie, 2010[9]	27 patients (10 male, age range 5-19 years, mean age 13.11 ±4.69) diagnosed by sweat test, genetic testing, or clinical signs	Ambiguous test results	Retrospective, cross-sectional study assessing effect of age, sex, FEV1, BMI, HbA1c, hospital admissions due to pulmonary problems, sputum culture, pulmonary arterial pressure on mortality	Mortality	n/a	Age, sex, FEV1, BMI, Hb were not related to mortality. Mean PAP was significantly lower in patients who died (40±15.1 vs. 68±11.5). Mortality was also associated with more hospital admissions in previous 6 months, and a 100% rate of Pseudomonas colonization (cf 50% for survivors)
Nguyen, 2010 [12]	51 adult CF patients (mean age 30.2 yrs.) in a French medical center	Having undergone cardiopulmonary exercise testing with blood gas analysis between 1997 and 2005.	Prospective cohort followed for at least 3 years; no control group	Mortality	n/a	In addition to BMI and diabetes, decreased FEV1, work rate, and higher alveolar-arterial gradient for O2 at peak exercise

Article ID / Cohort/First Author/Year	Participants (age, sex, condition)/ Sample size	Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Primary Outcome/ Method of Ascertainment	Study Quality/Applicability	Findings
						were associated with significantly increased risk for death. In multivariate analysis, the latter was independently associated with increased mortality when greater than 43mm Hg. Thus this measure may have prognostic value in adult CF patients.
Tonelli, 2010 [11]	57 consecutive adults (mean age 31.8±10 yrs) with CF at a US academic medical center	Having undergone evaluation for lung transplant	Cross-sectional	Pulmonary hypertension and mortality	n/a	Overall median follow-up time was 1.91 years; overall survival was 81% at 1 year, 61.4% at 3 years, and 47.7% at 5 years. At 5 years, 74% of patients had died or undergone lung transplantation. 36 patients with advanced lung disease (63.2%) had pulmonary hypertension (mean PAP≥25) and had significantly elevated

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						hypoxemia and O2 requirements. 5-year mortality was similar in patients with and without pulmonary HTN however, mortality was higher in patients with left ventricular ejection fraction <55%
QoL						
Tluczek, 2011[8]	95 CF patients, age 8-18 yrs (mean age 13.5±2.8)	Diagnosis via newborn screening (45 subjects) or by sweat or genetic testing (50 subjects)	Serial HRQOL questionnaire administered over 2 years	Association between QOL scores (physical and mental functioning, as assessed by the Cystic Fibrosis Questionnaire) and manifestations of pulmonary health		Early diagnosis group had more severe lung disease but differences disappeared when group differences in P. aeruginosa status and pancreatic status controlled for. 74% of patients had FEV1 values ≥80% predicted. Children<14: Worsening chest x-ray scores were associated with worse respiratory and physical domain scores on the QOL test. Children≥14: x-ray

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						scores associated with respiratory, health, and physical QOL domains, although changes in pulmonary health were not associated with changes in CFQ over time.
Epidemiological Study of Cystic Fibrosis (ESCF) Sawicki, 2011[10]	4 groups participants: 337 children (ages 6-13, mean age 8.9±2.0), 50% male 581 Parents (of the children) 398 Adolescents (ages 14-17, mean 15.3±1.1), 54% male 631 Adults (≥18, mean age 26.9±9.7)	None reported	Prospective observational study of CF patients at 261 sites in North America	Changes in CFQ-R and their association with changes health status/clinical characteristics over a one-year period (changes in respiratory signs/ symptoms cf changes in respiratory health domains; changes in nutritional health status cf. changes in nutritional health domains; changes in treatment complexity cf. changes in treatment burden scale		Few changes were observed over the 1-year period. Significant associations over time: increases in respiratory symptoms and worse CFQ-R respiratory symptom scores; declining weight and worsening CFQ-R nutritional health domains; increasing treatment complexity and worsening CRG-R Treatment Burden scores for parents. Thus although few changes seen, two patient-reported

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						outcomes were sensitive to changes in health status
Key Question 4: In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH? Adverse effects of interest include, but are not limited to, glucose intolerance, diabetes, and hypoglycemia.						
Stalvey, 2011[24]	See above			Adverse events associated with rhGH treatment of CF patients		100% of tx and 97% of controls reported at least one adverse event (AE). 12 participants in each group experienced a serious AE, mostly pulmonary exacerbations. 10 tx participants reported a study drug-related AE: 7 injection site reactions, 5 hyperglycemia (of whom 1 dropped out), 1 papilledema and headache (resulting in dropping out, most likely benign IH). 1 participant died of respiratory failure at 15 months, reported as

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						unrelated to study drug.
Key Question 5: What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (insulin-like growth factor-I [IGF-I] increases over 100 ng/ml or insulin –like growth factor binding protein-3 [(IGFBP-3] decreases over 1,000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2 mg/kg/week to 0.6 mg/kg/week) for disorders such as growth hormone deficiency (GHD) and idiopathic short stature (ISS)?						
Tang, 2012[23]	**1 15-year-old girl with primary GH deficiency treated with hGH for 17 months**	**Diagnosis of intracranial endodermal sinus tumors**	**Case study**	**CT, followed by surgical removal and histology**	**n/a**	**Rare germ-cell tumor not previously associated with hGH replacement. Temporal association but not possible to demonstrate causation**
Sävendahl, 2012[22] SAGhE Belgium/Netherlands / Sweden	**All patients in Sweden, the Netherlands, and Belgium diagnosed with isolated GH deficiency or idiopathic short stature or SGA who were enrolled in the SAGhe Study and began rhGH during childhood from 1985-**	**See participants**	**Observational**	**Data retrieved from national registries of GH-treated patients and national death registries in each country**	**n/a**	**21 deaths were identified. None were attributable to cancer.**

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	1997 and who reached 18 years of age by the (2,543 pts., for whom statistics were available for 90%)					
Carel, 2012[20] SAGhE France	6,928 children in France with idiopathic isolated GH deficiency (5162), neurosecretory dysfunction (534), idiopathic short stature (871) or SGA (335) who started hGH treatment between 1985 and 1996 (stats available for 94.7% in 1997)	See Participants	Observational	Data retrieved from national registries of GH-treated patients and national death registries in each country	n/a	Mortality rates were increased compared with non-GH treated children, particularly in those who received>50ug/kg-d. Increased rates of death due to bone cancer (SMR 5.00, 95% CI 1.01-14.63) but not all-type cancer mortality.
Child, 2011[21] Hypopituitary Control and Complications Study (HCCS)	6,840 GH-treated adults and 940 non-GH treated adults in the HCCS database;	See Participants	Observational, prospective cohort	Data retrieved from HCCS epidemiological database	n/a	Adults: With a mean follow-up of 3.7 years, 142 evident cancer cases were identified, for an overall

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	causes of GH deficiency varied, the majority resulted from brain tumors					**standardized incidence ratio of 0.88 (95% CI 0.74-1.04) for all countries included, 0.94 (95% CI 0.73-1.18) for the US cf. 1.16 (0.76-1.69) for non-GH-treated patients in the US. When cancer rates were examined among those under 35 and those with childhood onset GH-deficiency, rates were higher (3.79, 1.39-8.26; 2.74, 1.18-5.41, respectively)**
Mackenzie, 2011 [16]	All 224 patients treated with GH replacement therapy for at least 12 months after undergoing cranial irradiation over a 15-year period (for a brain tumor) at a	Patients lacking surveillance imaging data or complete x-ray dosing information were excluded.	Prospective cohort study	Incidence of recurrent or secondary tumors and mortality	n/a	Incidence of recurrent or secondary tumors did not differ between treated and untreated groups. Median latency time for detection of a meningioma was the same in both groups.

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	small UK hospital were considered eligible. 157 children and adults (mean age 33, range 14-45) were finally included, of whom 110 were able to be matched with controls. Patients were matched with controls not treated with GH.					Mortality was significantly higher in the control group than in the treated group (13.6 vs. 6.4%, p=0.03), but no significant difference in mortality by age at diagnosis of primary tumor..
Wilton, 2010 KIGS (Pfizer Database) [18]	KIGS database was established in 1987 to monitor children with growth disorders who are receiving rhGH. As of 8/08, database included 58,603 patients (197,173 patient years) with no Hx of neoplasm or other	Children in rhGH database with no prior history of cancer or condition that would increase risk of cancer	Prospective study: Children were followed from date of enrollment to last documented visit, date of report of cancer, or death	Development of a neoplasm as evidenced in medical records	n/a	From 1987 to 2008, new neoplasms reported in 32 KIGS patients with no known risk factors: 12 in males and 20 in females (7 of whom had Turners syndrome). Overall incidence of cancer in this cohort was similar to that in the general population (32 cases cf. 25 expected;

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	condition associated with increased risk for cancer.					standardized incidence ratio=1.26 [95% CI 0.86, 1.78)] No association was seen with type of growth disorder, GH dose, or serum IGFI levels
KIMS (Pfizer Database) Popovic, 2010[17]	Patients with malignancy: 100 of 180 patients with a de novo malignancy in the KIMS adult growth hormone deficiency database, Mean age 60.2±12.0 at Dx(41% females; Etiology of GH deficiency: 76 cases of pituitary adenoma) Controls: 325 patients with idiopathic GH deficiency, Mean age: 38.0±14.0 (39%	Affected cohort: Excluded non-melanoma skin cancers) for whom serum samples were available To ascertain that IGF-1 levels of controls were representative of patients without malignancies, IGF-1 levels were recorded for all KIMS patients for whom it had been measured (n=4,239)	Case-control study of individuals in maintenance phase of hGH treatment, aimed at maintaining IGF-1 levels within normal range. GH doses at baseline: 0.19-0.38mg/d GH doses closest to blood sample date: 0.30-0.54mg/d Malignancy, no means of ascertainment described. Serum samples drawn as closely as possible to Dx. RIAs used to measure Serum IGF-1, IGFBP-2 and IGFBP-3	AEs	n/a	When patients were stratified by age, no difference was seen between those with malignancies, those without, and the reference group, except in those under 40, for whom IGF-1 Z-scores were slightly higher in the group with malignancies (but n=10). IGFBP-2 and 3 Z-scores were higher in the malignancy group. In multivariate models that adjusted for age, sex, onset of GHD, and naivety to GH treatment at KIMS entry, the RR per unit IGF-1

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	females)					dropped to 1.02 and in a triple univariate model, it dropped to 0.96. The RR for the IGFBP remained significant. However, GH treatment had no effect on IGFBP levels, consistent with previous studies. Increased IGFBP may be the result of production by tumors.
KIMS Spielhagen, 2011[14]	Adult patients with GH deficiency treated with hGH 4-10 years (average 6.5 yrs) 216 women, 224 men consecutively documented Ages 20-49 years Primary causes of GH deficiency: tumor in >80% of cases	Not reported	Retrospective cohort study Mean dose GH at the end of the dose-finding phase (1 year): 0.43mg/d for women, 0.40mg/d for men Mean dose across all treatment period: 0.41mg/d for women, 0.37mg/d for men GH deficiency was ascertained at enrollment, IGF-1 levels were	AEs associated with rhGH	n/a	Low frequency of GH-associated AEs. 440 patients reported 40 AE most frequently associated with GH tx. Recurrence of pituitary or CNS tumors was reported in 6 (1.4%) patients; recurrence of other neoplasias: 11 (2.5%) patients; 6 patients developed DM during tx.

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			measured at baseline, year 1; AEs reported spontaneously, actively elicited by MDs, and drawn from labwork. Primary focus on most common GH-associated AEs			
National Cooperative Growth Study (NCGS), sponsored by Genentech Bell, 2010[15]	Pediatric patients with short stature (due to any cause) treated with rhGH followed over 20 years. Denominator ~55,000 children	NR	Retrospective cohort study of patients treated with Genentech rhGH	AE reports received from prescribing physicians, who are instructed to report any event potentially related to rhGH, and all instances of particular targeted events (new or recurrent malignancies and CNS tumors, DM, intracranial HTN (IH), slipped capital femoral epiphysis [SCFE], scoliosis, and pancreatitis). Frequencies compared to age-adjusted background rates in the general pediatric population. For the malignancy analysis, only new-	n/a	4,084 AE reports received as of 010106, of which 1,559 were serious AEs, including 174 deaths. Most were judged unrelated to hGH. Most common cause of death was CNS tumor (recurrence or new onset). 11% of deaths were judged to be related to rhGH by investigator (4 were not assessable and no causality was provided for 21). 19 of the 21 were due to neoplasms (1 osteosarcoma recurrence, the rest

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				onset tumors in individuals without increased risk were compared to general population (so essentially, prior malignancy, radiation exposure, etc. was excluded). For the DM analysis, only Type 1 was considered.		were CNS-related). Among particular groups (e.g., Prader Willi syndrome, Turner Syndrome, renal insufficiency), deaths due to particular causes may have been increased. Targeted AEs: DM: 37 Type 1; 20 Type 2; 8 unclassifiable (prob. Type 2). Standard incidence ratio (observed/expected for age-matched population)=0.90 (0.62, 1.26); could not calculate standard incidence ratio for Type 2, but incidence rate of ~14/100,000 Intracranial hypertension:61 confirmed cases; most resolved with discontinuation of drug; increased risk in Chronic Renal

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						Insufficency, Turner's Syndrome, Organic GHD SCFE:98 cases 68 unilateral, 25 bilateral); TS, OGHD, and CRI increased risk as did rapid growth, obesity, trauma, and radiation exposure Scoliosis:238 cases, 76 of which were pre-existing Pancreatitis:10 cases Adrenal insufficiency: 11 cases seen in patients with OGHD and idiopathic panhypopituitarism, 4 fatal 0 These findings support failure to confirm increased incidence of leukemia in patients without pre-existing risk

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						factors.
Key Question 6: In patients with CF, how are efficacy, effectiveness, safety, or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?						
No new studies						
Key Question 7: In patients with CF, how do the efficacy, effectiveness, safety, or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to, age (prepubertal, pubertal, postpubertal), gender, baseline clinical status (height, weight, LBM, pulmonary function, exercise tolerance, nutritional status), and/or the nature, extent, and effectiveness of prior treatment.						
No new studies						

Notes: DM diabetes mellitus; LBM lean body mass; SAGhE Safety and Appropriateness of Growth hormone Treatments in Europe Study; SMR standardized mortality rate

Appendix C. Questionnaire Matrix

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including pulmonary function; growth (height, weight, lean body mass [LBM], protein turnover), exercise tolerance, and bone mineralization, compared with usual care alone?			
Controlled trials were limited to patients with CF and impaired baseline growth indexes. Pulmonary Function: Five markers of pulmonary function were evaluated in patients with CF receiving rhGH therapy. In controlled trials, the forced expiratory vital capacity (FVC) and percent predicted FVC significantly increased from baseline in CF receiving chronic rhGH therapy vs. control therapy. Single-arm observational studies support these findings. In controlled trials, the forced expiratory volume) FEV_1 significantly increased from baseline in patients with CF receiving chronic rhGH therapy vs. control therapy, while the percent predicted FEV_1 showed no significant differences vs. control. Single-arm observational studies support the FEV_1 findings, but the findings on percent predicted FEV_1 are mixed. In one available controlled trial, no change in FEV_1 Z-score occurred in patients receiving rhGH for CF vs. placebo therapy and no observational	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
studies evaluated this parameter.			
Anthropometric Measures: In controlled trials suitable for pooling, significant improvements in height were observed for patients with CF receiving rhGH therapy vs. control therapy as measured by the change in height, height velocity, height Z-score, and height percentile. Observational studies or other trials not suitable for pooling support these findings. In controlled trials, significant improvements in weight were observed for patients with CF receiving rhGH therapy vs. control therapy as measured by change in weight, weight velocity, body mass index (BMI), percent ideal body weight (IBW), lean body mass (LBM), and weight percentile. Patients receiving rhGH therapy had a trend toward a higher weight Z-score but did not have a higher BMI Z-score than those receiving control therapy. Observational studies evaluating change in weight, weight velocity, and weight Z-score were generally supportive of improvements associated with rhGH therapy, although one crossover trial not amenable to pooling did not show any improvement in LBM in patients receiving rhGH compared with those who received glutamine therapy.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Protein Turnover: Four markers of protein turnover were evaluated in patients with CF receiving rhGH therapy. In controlled trials, rhGH therapy significantly improved two markers of protein turnover (rate of leucine oxidation [LeuOx] and rate of nonoxidative leucine disappearance [NOLD]) and had no effect on leucine rate of appearance (LeuRa) concentrations. In one observational trial, nitrogen balance was qualitatively impacted but protein synthesis was unchanged.	☐	New Evidence:	☐
Exercise Tolerance: In controlled trials, rhGH therapy significantly improved exercise workrate. Qualitative improvements in several measures of exercise tolerance were seen after rhGH therapy in patients with CF but in most cases do not reach statistical significance. Given the few trials evaluating this type of endpoint and the various makers being evaluated, the impact is difficult to determine at this time.	☐	New Evidence:	☐
Bone Maturation: In controlled trials and single-arm observational studies, treating patients with rhGH therapy does not improve bone age in patients with CF. However, bone mineral content does significantly improve with rhGH therapy in trials, and bone mineral content Z-score was also improved in one trial in which it was assessed.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Sexual Maturation: In patients with CF, rhGH therapy does not seem to improve sexual maturation in males and the impact in females cannot be determined at this time. Controlled trials were not amenable to pooling, and no single-arm observational data were available. In five controlled trials, rhGH therapy did not improve sexual maturation regardless of gender. In one controlled trial, mean Tanner stage improved regardless of gender, and in an analysis of three controlled trials, rhGH therapy significantly improved sexual maturation in females but not in males.	☐	New Evidence:	☐
Overall Conclusions: **In patients with CF and impaired baseline growth indexes, rhGH improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF vs. control.**			
Key Question 2: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including frequency of required intravenous antibiotic treatments, frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia, or mortality, compared with usual care alone?			
There is insufficient evidence to determine the effect of rhGH on final health outcomes. Preliminary data suggest that rhGH may have benefit regarding intravenous antibiotic use. However, there is insufficient evidence to determine the effect of rhGH on pulmonary exacerbations, HRQoL, bone consequences, or mortality. There is moderate evidence to suggest that rhGH therapy reduces the rate of hospitalization.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Overall Conclusions: **Improvements in bone mineral content vs. control are also promising. However, with the exception of hospitalizations, the benefits on final health outcomes cannot be directly determined at this time.**			
Key Question 3: In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?			
Mortality and Pulmonary Function: The association between pulmonary function and mortality in patients with CF was evaluated in 28 studies. Only one of three studies that evaluated FVC at baseline and mortality found a univariate association,, and only two of five that evaluated percent predicted FVC at baseline and mortality found a univariate association. However, only one of the aforementioned studies performed multivariate analysis; that study found that percent predicted FVC at baseline was a multivariate predictor. Decrease in FVC was a univariate and multivariate predictor of mortality in two trials but not in two other trials. Some studies using univariate analysis found an association between measures of absolute FEV_1 and mortality, but other studies did not. In the only two multivariate analyses, an association was found between FEV_1 and mortality in one study, but no association was seen between the decline in FEV_1 and mortality in one study. The link between percent predicted FEV_1 and mortality is	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
stronger, with the majority of studies finding an association between percent predicted FEV_1 and mortality.			
Mortality and Anthropometrics: The association between anthropometrics and mortality in patients with CF was evaluated in 26 studies. The link between height and mortality is weak with only a minority of studies reporting an association. The link between different measures of weight and mortality was supported in a majority of studies that performed univariate analysis. Only one study found a multivariate relationship between weight and mortality, and another multivariate analysis did not. The link between BMI and mortality is controversial, with some studies showing no association, others showing only a univariate association, and very few showing a multivariate association. The link between IBW and mortality was supported by several univariate associations and in the only multivariate analysis. The only study evaluating the association between percent predicted weight-for-height and mortality found a multivariate association.	☐	New Evidence:	☐
Mortality and Protein Turnover: No studies evaluated the association between protein turnover and mortality.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Mortality and Exercise Tolerance: The association between exercise tolerance and mortality in patients with CF was evaluated in 10 studies. The link between walk testing and mortality is weak, with some studies finding no association, some finding only a univariate association, and very few finding a multivariate association. The link between peak oxygen uptake during exercise testing and mortality was supported only by univariate analyses.	☐	New Evidence:	☐
Mortality and Bone Mineralization: No studies evaluated the association between bone mineralization and mortality.	☐	New Evidence:	☐
Health-related Quality of Life (HRQoL) and Pulmonary Function: The association between pulmonary function and HRQoL in patients with CF was evaluated in 14 studies, but 10 different scales were used. All studies but one specified that they explored the association between percent predicted FEV_1 and HRQoL. The last study did not specify whether the FEV_1 was the absolute or percent predicted. Only four studies employed multivariate analyses (each using different questionnaires to rate HRQoL). In one multivariate analysis, higher percent predicted FEV_1 was associated with improvements in "ways of coping" but not subjective health perception, and it was not specified whether absolute or percent	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
predicted FEV_1 was used. Higher percent predicted FEV_1 was associated with improvements in seven of nine health domains (including social and physical functioning and chest symptoms) in another study and with general well-being in another study, but no association was seen between FEV_1 and general health perception in the final study.			
HRQoL and Anthropometrics: The association between anthropometrics and HRQoL in patients with CF was evaluated in 10 studies, but nine different scales and different anthropometric parameters were used. Only fives studies employed multivariate analyses (each using different questionnaires to rate HRQoL). In multivariate analysis, greater percent IBW was not associated with subjective health perception or coping in one study; greater IBW was not associated with subjective health perception or coping in one study; greater BMI was associated with improvements in body image but not any other factor, including social and physical functioning and chest symptoms, in another study; adequate weight gain over 2 years was associated with improvements in physical functioning but not other social or emotional functioning; BMI Z-score was not associated with any of the three dimensions in one study; greater BMI was associated with lower general health perception in one study; and BMI was not associated with life satisfaction.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
HRQoL and Protein Turnover: No studies evaluated the association protein turnover and HRQoL.	☐	New Evidence:	☐
HRQoL and Exercise Tolerance: Two studies evaluated the association between exercise tolerance and HRQoL using two different questionnaires. Greater exercise capacity (determined by peak oxygen uptake [VO_{2peak}] or maximal workload) is associated with better measures of HRQoL scores in univariate analyses.	☐	New Evidence:	☐
HRQoL and Bone Mineralization: No studies evaluated the association between bone mineralization and HRQoL.	☐	New Evidence:	☐
Bone Consequences and Pulmonary Function/Anthropometrics: Only one study evaluated the association between pulmonary function or anthropometrics and bone consequences. In univariate analyses, there was no relationship between FEV_1, FVC, or BMI and bone	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
fracture.			
Bone Consequences and Protein Turnover/Exercise Tolerance/Bone Mineralization: No studies evaluated the association between protein turnover, exercise tolerance, or bone mineralization and bone consequences.	☐	New Evidence:	☐
Key Question 4: In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH? Adverse effects of interest include, but are not limited to, glucose intolerance, diabetes, and hypoglycemia.			
In two controlled trials suitable for pooling, therapy with rhGH did not impact Hemoglobin A1c in CF patients vs. control. In CF patients, rhGH therapy significantly increased fasting blood glucose concentrations vs. control in three controlled trials but did not significantly alter random, postprandial, and stimulated blood glucose concentrations vs. control or baseline. Most CF patients receiving rhGH in five controlled and three single-arm observational studies did not develop glucose intolerance or diabetes over the duration studied (6-12 months). The strength of evidence was moderate for the fasting blood glucose evaluation; low for the A1c, glucose intolerance, and diabetes mellitus evaluations; and insufficient for the other endpoints.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
In CF patients receiving rhGH, injection site reactions were a rare adverse effect reported in observational studies. CF patients on rhGH rarely experienced a transient increase in liver transaminases in two single-arm observational studies. Study withdrawals were rarely reported in the nine trials with evaluable data, and withdrawals in patients with CF receiving rhGH were similar to control. These endpoints could not be rated for strength of evidence given the paucity of data available.	☐	New Evidence:	☐
Overall Conclusions: **In the relatively low doses used in CF patients for a time period of 6-12 months, rhGH therapy may worsen short-term markers of glucose control but has no effect on A1c vs. control.**			
Key Question 5: What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (insulin-like growth factor-I [IGF-I] increases over 100 ng/ml or insulin –like growth factor binding protein-3 [(IGFBP-3] decreases over 1,000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2 mg/kg/week to 0.6 mg/kg/week) for disorders such as growth hormone deficiency (GHD) and idiopathic short stature (ISS)?			
IGF-1 Levels; In patients with CF, there appears to be an increase in IGF-I levels in patients treated with rhGH compared to control, but the strength of evidence is insufficient. IGFBP-3 Levels: There is insufficient evidence to determine	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
the impact of rhGH treatment on IGFBP-3 levels. Cancer Risk: In patients with growth hormone deficiency (GHD) or idiopathic shortness of stature (ISS), there is little evidence to evaluate the effects of rhGH treatment on cancer risk.			
Overall Conclusions: **The increase in IGF-I with rhGH therapy is above a threshold thought to increase the risk of malignancy, but the strength of this marker in determining malignancy is not firmly established. A time period of 6-12 months may be insufficient to determine the effect of rhGH on development of diabetes or malignancy.**			
Key Question 6: In patients with CF, how are efficacy, effectiveness, safety, or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?			
Dose-Response: Only one trial provided insight into the dose-response nature of rhGH in patients with CF. In this trial, no significant differences were seen between the higher and the lower dose groups for any evaluated parameter.	☐	New Evidence:	☐
Duration: Several trials varied in the duration of rhGH therapy, allowing subgroup analysis based on therapy duration. Trials with 1 year of rhGH therapy significantly increased percent predicted FVC, absolute FEV_1, and height compared to control, while 6 months of rhGH	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
therapy showed no effect. Trials with 1 year of rhGH therapy significantly increased fasting glucose concentrations, while trials of 6 months duration showed no effect.			
Nutritional Deficiencies: Use of rhGH has not been studied in patients with CF who have nutritional deficiencies that are not being addressed with enteral nutrition. We cannot determine the benefits of rhGH therapy in patients with unaddressed nutritional deficiencies.	☐	New Evidence:	☐
Concurrent Medical Therapies: The use of concurrent medical therapies in patients in controlled trials evaluating rhGH therapy was sparingly reported, so the differential effect on rhGH efficacy could not be assessed.	☐	New Evidence:	☐
Key Question 7: In patients with CF, how do the efficacy, effectiveness, safety, or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to, age (prepubertal, pubertal, postpubertal), gender, baseline clinical status (height, weight, LBM, pulmonary function, exercise tolerance, nutritional status), and/or the nature, extent, and effectiveness of prior treatment.			
Age: A patient's age may impact rhGH efficacy, as seen in an analysis with individual patient data merged and in a subgroup analysis. In an analysis of trials with individual patient data merged, both prepubertal and adolescent patients had significant improvements in height, weight, LBM, and hospitalizations compared with their respective control populations. Prepubertal patients receiving rhGH did not have significant increases in FEV_1, and the percent predicted FEV_1 was significantly lower than for prepurbertal	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
control patients. In contrast, adolescent patients receiving rhGH had significant improvements in FEV_1 and percent predicted FEV_1 compared with adolescent control patients.			
When we pooled studies limited to prepubertal patients and then pooled the trials limited to pubertal patients, we noted some difference in magnitude of effect with rhGH vs. control between populations. Given inherent limitations in cross- evaluating between these two controlled study types, the following observations should be viewed only as hypothesis-generating. Compared with pubertal patients receiving rhGH, prepubertal patients receiving rhGH seem to derive greater benefits in height vs. control but lesser benefits in weight, BMI, and percent IBW vs. control. Compared with prepubertal patients receiving rhGH, pubertal patients receiving rhGH seem to derive greater increases in absolute FVC, FEV_1, and bone mineral content vs. control but experience fewer hospitalizations and smaller increases in percent predicted FVC.	☐	New Evidence:	☐
Gender: While trials were conducted predominantly in males, the impact of gender on outcomes of rhGH therapy could be evaluated in one pooled analysis. The authors of the analysis did not report p-values or whether the comparisons were statistically significant and did not provide patient numbers, precluding our ability to calculate these p-values. In	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
prepubertal patients not receiving rhGH therapy, no difference in height velocity occurred between the genders in the year before treatment allocation, but females had greater weight velocity. In pubertal patients not receiving rhGH therapy, females had greater height and weight velocity than males in the year before treatment allocation. In prepubertal patients, the first 6 months of rhGH therapy provided similar increases in height and weight velocity between genders, but in months 6-12, females had greater height velocity while males had greater weight velocity. In pubertal patients, the first 6 months of rhGH therapy provided similar increases in height velocity between genders, but females had greater increases in weight velocity. In months 6-12, females had greater height and weigh velocities than males. The occurrence of adverse effects associated with rhGH therapy in males and females was not individually determined.			
The impact of baseline clinical status on the clinical outcomes of rhGH use was assessed in two trials. In the first trial, those with a baseline height Z-score below -2.2 had a similar increase in height Z-score on rhGH therapy. In the second trial, a higher baseline percent predicted FEV_1 was positively correlated with the change of weight associated with rhGH therapy. The occurrence of adverse events associated with rhGH therapy in patients with different	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
baseline clinical status could not be determined.			
Are there new data that could inform the key questions that might not be addressed in the conclusions?			